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A section of the Anatomical Therapeutic Chemical Classification System.

N Nervous system

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N02A Opioids

N02AA Natural opium alkaloids

N02AA01 Morphine
N02AA02 Opium
N02AA03 Hydromorphone
N02AA04 Nicomorphine
N02AA05 Oxycodone
N02AA08 Dihydrocodeine
N02AA09 Diamorphine
N02AA10 Papaveretum
N02AA51 Morphine, combinations
N02AA58 Dihydrocodeine, combinations
N02AA59 Codeine, combinations excluding psycholeptics
N02AA79 Codeine, combinations with psycholeptics

N02AB Phenylpiperidine derivatives

N02AB01 Ketobemidone

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N02AB02 Pethidine
N02AB03 Fentanyl
N02AB52 Pethidine, combinations excluding psycholeptics
N02AB72 Pethidine, combinations with psycholeptics

N02AC Diphenylpropylamine derivatives

N02AC01 Dextromoramide
N02AC03 Piritramide
N02AC04 Dextropropoxyphene
N02AC05 Bezitramide
N02AC52 Methadone, combinations excluding psycholeptics
N02AC54 Dextropropoxyphene, combinations excluding psycholeptics
N02AC74 Dextropropoxyphene, combinations with psycholeptics

N02AD Benzomorphan derivatives

N02AD01 Pentazocine
N02AD02 Phenazocine

N02AE Oripavine derivatives

N02AE01 Buprenorphine

N02AF Morphinan derivatives

N02AF01 Butorphanol
N02AF02 Nalbuphine

N02AG Opioids in combination with antispasmodics

N02AG01 Morphine and antispasmodics
N02AG02 Ketobemidone and antispasmodics
N02AG03 Pethidine and antispasmodics
N02AG04 Hydromorphone and antispasmodics

N02AX Other opioids

N02AX01 Tilidine
N02AX02 Tramadol
N02AX03 Dezocine
N02AX52 Tramadol, combinations

N02B Other analgesics and antipyretics**N02BA Salicylic acid and derivatives**

N02BA01 Acetylsalicylic acid
N02BA02 Aloxiprin
N02BA03 Choline salicylate

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Opioid

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An **opio**id is any agent that binds to opioid receptors, found principally in the central nervous system and gastrointestinal tract. There are four broad classes of opioids: endogenous opioid peptides, produced in the body; opium alkaloids, such as morphine (the prototypical opioid) and codeine; semi-synthetic opioids such as heroin and oxycodone; and fully synthetic opioids such as pethidine and methadone that have structures unrelated to the opium alkaloids.

Although the term *opiate* is often used as a synonym for *opioid*, it is more properly limited to the natural opium alkaloids and the semi-synthetics derived from them.

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Pharmacology

Main article: opioid receptor

Opioids bind to specific opioid receptors in the central nervous system and in other tissues. There are at least four major classes of opioid receptors: μ , κ , δ and possibly σ . In addition, there are two subtypes of μ receptor: μ_1 and μ_2 . These are all G-protein coupled receptors acting on GABAergic neurotransmission. The pharmacodynamic response to an opioid depends on which receptor it binds, its affinity for that receptor, and whether the opioid is

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an agonist or an antagonist. For example, the supraspinal analgesic properties of the opioid agonist morphine are mediated by activation of the μ_1 receptor, respiratory depression and physical dependence (dependency) by the μ_2 receptor, and sedation and spinal analgesia by the κ receptor.

Overdose

Opioid overdose can be rapidly reversed with an opioid antagonist such as naloxone or naltrexone. These competitive antagonists bind to the opioid receptors with higher affinity than agonists but do not activate the receptors. This displaces the agonist, attenuating and/or reversing the agonist effects. However, the elimination half-life of naloxone can be shorter than that of the opioid itself, so repeat dosing or continuous infusion may be required.

Tolerance, Dependence, Addiction, and Abuse

Tolerance is the tendency of the body to adapt to the presence of opioids; this adaptation makes it necessary to use ever-increasing doses of opioids in order to achieve the same effects. Tolerance is more pronounced for some effects than for others.

Dependence is the tendency of the body to manifest a characteristic and unpleasant *withdrawal syndrome* if regular doses of opioids are abruptly discontinued after tolerance has developed.

Addiction is a psychological attachment to certain effects of opioids (such as the euphoria that many people experience when the drugs are taken in sufficiently large doses) that drives some people to take the drugs even when they are not medically necessary, and even when their use of the drugs becomes self-destructive. Dependency and the unpleasantness of withdrawal can work to maintain addiction, although they do not cause it.

All persons receiving opioids for any reason will develop some degree of tolerance and dependence over time. Some people will also develop addiction. Addiction is much more common in persons taking opioids purely for non-medical reasons (such as recreation); it rarely develops in persons who are taking opioids under medical supervision for legitimate therapeutic purposes (such as pain management), particularly when the dosage used is too low to produce any feeling of euphoria.

Abuse is the misuse or overuse of opioids; the phenomena of tolerance and dependency, combined with the addictive potential presented by some effects of opioids (such as euphoria), make these drugs prime candidates for drug abuse. This is why the medical and especially the recreational (and usually illicit) use of opioids are so controversial. Unfortunately, as previously mentioned, opioids remain the most effective analgesics available, and so there are very strong arguments for their continued use, at least in medicine.

Of note, current nomenclature within the field of Psychiatry (see DSM-IV) is to use the term "Dependence" to refer to the condition of "Addiction" as defined above. As a result, a psychiatric diagnosis of opioid dependence does not imply that a withdrawal syndrome is imminent if opioids are discontinued, though such a situation could be present. This nomenclature is being reconsidered for DSM-V, expected to be published in 2011.

However, the commonly accepted notion that opioids 'cause addiction' has been disputed, especially given the large economic advantages of the War on Drugs [1] (<http://www.parl.gc.ca/37/1/parlbus/commbus/senate/comm-e/ille-e/presentation-e/alexander-e.htm>).

Uses

Clinical use

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Opioids are widely used in medicine as strong analgesics (pain relievers). Despite extensive research, no other analgesics have yet been found that are more effective for severe pain. One of the advantages of opioids is that there is no upper limit to the dosage and the achievable pain relief as long as the dose is increased gradually to allow tolerance to develop to adverse effects (especially respiratory depression).

Opioids have long been used to treat acute pain (such as post-operative pain). They have also found to be invaluable in palliative care to alleviate the severe, chronic, disabling pain of terminal conditions such as cancer. Very high doses are often required in palliation to improve the patients' terminal quality-of-life.

In recent years there has been an increased use of opioids in the management of non-malignant chronic pain. While this trend is still somewhat controversial in some circles, due to issues of dependence, the emerging medical consensus is that most chronic pain patients can safely use opioids for years with a minimal risk of addiction or toxicity and that the overall increase in quality of life outweighs any adverse effects of opioid use.

As recently as the early 20th century, opioids were administered by doctors to treat severe depression and other psychiatric disorders. The practice was discontinued because of the addictive potential of opioids. In recent decades, researchers have experimented with mixed opioid agonist/antagonists such as buprenorphine for the treatment of depression and other psychiatric disorders, encouraged by the decreased liability toward abuse of and dependence on these compounds, compared with full opioid agonists.

United States

The sole clinical indications for opioids in the US, according to *Drug Facts and Comparisons*, 2005, are

- Analgesia and anesthesia
- Cough (codeine and hydrocodone only)
- Diarrhea (opium only)
- Anxiety due to shortness of breath (oxymorphone only)
- Detoxification (methadone only)

Opioids are prohibited for psychological relief (with the narrow exception of anxiety due to shortness of breath), despite their extensively reported psychological benefits. The prohibition has no therapeutic basis; its basis is fear of addiction and diversion. The prohibition allows no exceptions, even when opioids might be especially effective and when the possibility of addiction or diversion is very low — for example, in the treatment of senile dementia, geriatric depression, and psychological distress due to chemotherapy or terminal diagnosis.

Recreational use and abuse

Most opioids produce euphoria in many people when ingested orally, intravenously, subcutaneously, rectally, through the nasal membranes, or when smoked. Recreational use and abuse of opioids usually is motivated by a desire to experience this euphoria, and it can easily lead to addiction. Tolerance to euphoria develops rapidly; a regular user may require significantly higher and higher dosages of the substance in order to achieve the desired effect. Opioids' ability to block pain, both physical and emotional, can also encourage abuse and addiction. Some recreational users are able to moderate their usage, balancing the cost of using against the pleasure and other desirable effects, and some believe that such responsible use (which wouldn't harm the user or anyone else), should be allowed by law.

Typically, persons taking opioids under medical supervision for the usual clinical purposes (such as pain management) are less likely to develop addictions or patterns of abuse than those who begin using the drug specifically for its other effects such as euphoria. However it is very likely that many addicts began using because

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they experienced the great relief from some types of "psychological pain" that only opiates can provide.

History

Non-clinical use and off-label clinical use were criminalized in the USA by the Harrison Narcotics Tax Act of 1914, and by other laws worldwide. Since then, nearly all non-clinical use and off-label clinical use of opioids has been rated zero on the scale of approval of nearly every social institution. (However, in UK the 1926 report of the Departmental Committee on Morphine and Heroin Addiction under the Chairmanship of the President of the Royal College of Physicians reasserted medical control and established the "British system" of control — which lasted until the 1960s; in the US the Controlled Substances Act of 1970 markedly relaxed the harshness of the Harrison Act, yet still the laws remain extremely harsh. Respectable, responsible heroin users are frequently given extremely long prison sentences while rapists often spend far less time in jail)

Before the twentieth century, institutional approval was often higher, even in Europe and America. In some cultures, approval of opioids was significantly higher than approval of alcohol.

Today those who approve of at least some non-clinical use claim that opioids are not more addictive than alcohol; that opioids do not cause the physical damage that alcohol does (cirrhosis, domestic violence, etc.); and that approval of opioids in those cultures that approved them was earned by abuse rates well below those associated with alcohol.

For example, Andrew Weil says in *From Chocolate to Morphine: Understanding Mind-Active Drugs* that tolerance to and withdrawal from opioids is "less hazardous than [tolerance to and] withdrawal from sedative-hypnotics. ... People can take opiates every day for years and remain in good health, provided they keep up good habits of hygiene and nutrition. There are many documented cases of opium and morphine addicts who, despite lifelong, heavy habits, survived to ripe old ages, remaining healthy to the end. ... The worst medical effect of regular opiate use is severe and chronic constipation."

Today those who approve of non-clinical use of opioids often prefer the term *recreational* for such use. Non-clinical occasional or light users are sometimes known as *chippers*.

Opponents of non-clinical use point to another of its detrimental effects: apathy (an often-mentioned attribute of the habitués of opium dens) and consequent social decay. This is however a stereotype and this argument is completely null. Most opiate users need opiates to function, and when they have opiates they are happy and productive people. You might have known someone for years who is dependent on opiates, and yet you wouldn't have the slightest idea of it.

Adverse effects

Opioids are associated with a range of adverse drug reactions - mostly associated with their pharmacological actions at opioid receptors.

Common adverse reactions include: nausea and vomiting, drowsiness, dizziness, headache, orthostatic hypotension, itch, dry mouth, miosis, urinary retention, and constipation. (Rossi, 2005)

Infrequent adverse reactions include: dose-related respiratory depression (see below), confusion, hallucinations, delirium, urticaria, hypothermia, bradycardia/tachycardia, ureteric or biliary spasm, muscle rigidity, myoclonus (with high doses), and flushing (due to histamine release, except fentanyl and remifentanyl). (Rossi, 2005).

The most serious adverse reaction associated with opioid use is respiratory depression. This can occur with a

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single dose. Although tolerance develops rapidly, respiratory depression is the mechanism behind the fatal consequences of overdose.

Chronic use of opioids may result in serious constipation, which may progress to bowel obstruction, fecal impaction, or paralytic ileus. Because these conditions may require surgical intervention, stimulant laxatives are generally given as an adjunct to prevent these complications. Physiological tolerance does not develop with regard to constipation. It should be noted that in some therapeutic regimens (such as those aimed at treating diarrhea), mild constipation is a desired effect and hence laxatives would not be given.

Both therapeutic and chronic use of opioids can compromise the function of the immune system. Opioids decrease the proliferation of macrophage progenitor cells and lymphocytes, and affect cell differentiation. (Roy & Loh, 1996) Opioids may also inhibit leukocyte migration.

Tolerance

Tolerance can be detected within 12-24 hours of the administration of morphine (Rang *et al.*, 2003), and similarly for some other opioid agonists. Tolerance results in the necessity for increasing the dose over time to achieve the desired clinical effect.

Tolerance appears to develop first to the analgesic, sedative, emetic, euphoric and respiratory depressive effects of opioids. The miotic and constipating effects are more resistant to the development of tolerance. (Rang *et al.*, 2003)

Dependence and withdrawal issues

Regular use of an opioid for any reason rapidly induces physical dependence, characterized by a highly unpleasant withdrawal syndrome when the drug is discontinued or rapidly reduced in dosage, or when an antagonist is administered. The acute withdrawal syndrome generally consists of signs and symptoms opposite to those of the drug when initially administered: severe dysphoria, anxiety, eye tearing, a runny nose, goose bumps, sweating, nausea, vomiting, cramps and deep pains are common. The speed and severity of withdrawal depends on the half-life of the opioid—heroin withdrawal occurs more quickly and is more severe than methadone withdrawal, but methadone withdrawal takes longer. The acute withdrawal phase is often followed by a protracted phase of depression and insomnia that can last for months.

Physical dependence is distinct from and does not imply psychological addiction, defined as uncontrolled drug use despite harm. However, physical dependence can aggravate psychological addiction when it occurs.

Some patients with narcotic dependence experience recurrent episodes of severe abdominal pain and nausea leading to hospitalizations and extensive diagnostic workups over periods of months to years. The intractable nausea resolves when the pain is treated with narcotics, the patient is able to go home, but another episode recurs when the pain medication runs out.

Withdrawal symptoms can be minimised by slowly tapering the dose over days or weeks, sometimes after switching to a long-acting opioid such as methadone. The symptoms of opioid withdrawal can also be treated with other medications, such as clonidine for sympathetic hyperactivity and a benzodiazepine for anxiety and insomnia.

"Rapid detox" is a relatively new technique that uses opioid antagonists to cause acute withdrawal while the patient is under general anesthesia to eliminate the otherwise extreme discomfort. This procedure has attracted controversy due to its high cost and risk; several patients have died during the procedure. Many pain specialists

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think that the procedure is unnecessary, and addiction specialists criticize it for doing nothing to keep an addict from relapsing into opioid abuse after the procedure is complete. Indeed, there have been reports of addicts undergoing rapid detox with the full intention of resuming addiction as the technique drastically reduces tolerance thus reducing the cost of addiction. Rapid detox also does not alleviate the protracted withdrawal syndrome that lasts for weeks or months after the acute phase.

Although physical dependence is nearly universal among those who use opioids regularly, true addiction is quite rare even when large amounts of opioids are used over long periods of time to treat chronic pain under the close supervision of a doctor. This is thought to be because of the rapid development of tolerance to the euphorogenic properties of opioids; without euphoria, only the unpleasant side effects (such as bowel dysfunction) remain, so there is no motivation to take more than is needed to manage pain.

Examples of opioids

Endogenous opioids

Opioid-peptides that are produced in the body:

- Endorphins
- Dynorphins
- Enkephalins

Dynorphin Acts through κ -opioid receptors, and is widely distributed in the CNS, including in the spinal cord and hypothalamus, including in particular the arcuate nucleus and in both oxytocin and vasopressin neurons in the supraoptic nucleus.

[met]-enkephalin is widely distributed in the CNS; [met]-enkephalin is a product of the proenkephalin gene, and acts through μ and δ -opioid receptors.

[leu]-enkephalin, also a product of the proenkephalin gene, acts through δ -opioid receptors

Nociceptin, formerly known as orphanin FQ, is an opioid-related peptide, but it does not act at the classic opioid receptors and actions are not antagonised by the opioid antagonist naloxone. Nociceptin is a potent anti-analgesic. Nociceptin is widely distributed in the CNS; it is found in many regions of the hypothalamus, brainstem, forebrain, as well as in the ventral and dorsal horns of the spinal cord. Nociceptin acts at the NOP1 receptor, formerly known as ORL-1. The receptor is also widely distributed in the brain, including in the cortex, anterior olfactory nucleus, lateral septum, hypothalamus, hippocampus, amygdala, central gray, pontine nuclei, interpeduncular nucleus, substantia nigra, raphe complex, locus coeruleus, and spinal cord.

Endomorphin. Acts through μ -opioid receptors, and is more potent than other endogenous opioids at these receptors.

β -endorphin is expressed in POMC cells in the arcuate nucleus and in a small population of neurons in the brainstem, and acts through μ -opioid receptors. β -endorphin has many effects, including on sexual behavior and appetite. β -endorphin is also secreted into the circulation from pituitary corticotropes and melanotropes. α -neoendorphin is also expressed in POMC cells in the arcuate nucleus

Opium alkaloids

Phenanthrenes naturally occurring in opium:

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- Morphine
- Codeine
- Thebaine

Preparations of mixed opium alkaloids, including papaveretum, are still occasionally used.

Semisynthetic derivatives

- Diacetylmorphine (heroin)
- Oxycodone
- Hydrocodone
- Dihydrocodeine
- Hydromorphone
- Oxymorphone
- Nicomorphine

Synthetic opioids

Phenylheptylamines

- Methadone
- Levo-alphaacetylmethadol (LAAM)

Phenylpiperidines

- Pethidine (meperidine)
- Fentanyl
- Alfentanil
- Sufentanil
- Remifentanyl
- Ketobemidone
- Carfentanyl

Diphenylpropylamine derivatives

- Propoxyphene
- Dextropropoxyphene
- Dextromoramide
- Bezitramide
- Pir tramide

Benzomorphan derivatives

- Pentazocine
- Phenazocine

Oripavine derivatives

- Buprenorphine

Morphinan derivatives

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- Butorphanol
- Nalbupine
- Levorphanol
- Levomethorphan

Others

- Dezocine
- Etorphine
- Lefetamine
- Tilidine
- Tramadol
- Loperamide (used for diarrhoea, does not cross the blood-brain barrier)
- Diphenoxylate (used for diarrhoea, does not appreciably cross the blood-brain barrier)

Opioid antagonists

- Naloxone
- Naltrexone

See also

- Psychoactive drug

External links

- American Pain Foundation (<http://www.painfoundation.org/>)
- American Pain Society (<http://www.ampainsoc.org/>)
- American Academy of Pain Management (<http://www.aapainmanage.org/>)
- American Academy of Addiction Psychiatry (<http://www.aaap.org/>), professional association of psychiatrists expert in addiction treatment
- Poppies.org (<http://www.poppies.org/>)
- Heroin Helper (<http://www.heroinhelper.com/>)
- Future Opioids (<http://opioids.com/>)
- The use of opioids for chronic pain @ The APS (<http://www.ampainsoc.org/advocacy/opioids.htm>)
- Merck Entry on Opioids (<http://www.merck.com/mmhe/sec07/ch108/ch108c.html>)

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Opioids

Alfentanil, Anileridine, Buprenorphine, Butorphanol, Carfentanil, Codeine, Codeinone, Dextropropoxyphene, Diamorphine (Heroin), Dihydrocodeine, Etorphine, Fentanyl, Hydrocodone, Hydromorphone, Loperamide, Methadone, Morphine, Morphinone, Nalbuphine, Oxycodone, Oxymorphone, Pentazocine, Pethidine (Meperidine), Remifentanil, Sufentanil, Tramadol

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